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बौद्धिक सम्पदा भारत

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भौगोलिक संकेत

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सत्यमेव जयते

भारत सरकार / GOVERNMENT OF INDIA

पेटेंट कार्यालय / THE PATENT OFFICE

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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Application and Provisional Specification filed on 11/03/04 in respect of Patent Application No.304/MUM/2004 of SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI - 400 059, INDIA.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 11th day of July 2005.

(A. T. PATRE)

ASSTT. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 OF 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

We, SUN PHARMACEUTICAL INDUSTRIES LTD., ACME PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059, INDIA

AN INDIAN COMPANY

hereby declare -

- (i) that we are in possession of an invention titled "A PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-10-OXO-5H-DIBENZ[B,F]AZEPINE-5-CARBOXAMIDE"
- (ii) that the provisional specification relating to this invention is filed with this application.
- (iii) that there is no lawful ground of objection to the grant of a patent to us.

We, further declare that the inventors for the said invention are

1) Mrs. Muthukumaran Mandakini 2) Mr. Natarajan Muthukumaran
3) Dr. Thennati Rajamannar. of SUN PHARMA ADVANCED RESEARCH CENTRE, AKOTA ROAD, AKOTA, BARODA 390020, GUJARAT, INDIA; an Indian national.

We claim the priority from the applications filed in convention countries, particulars of which are as follows: Not Applicable

We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: Not Applicable

We state that the application is divided out of our application, the particular of which are given below and pray that this application deemed to have been filed under section 16 of the Act: Not Applicable

That we are the assignee of the true and first inventors.

That our address for service in India is as follows-

Dr. RATNESH SHRIVASTAVA,
INTELLECTUAL PROPERTY CELL,
SUN PHARMACEUTICAL INDUSTRIES LTD,
ACME PLAZA, ANDHERI-KURLA ROAD,
ANDHERI (E), MUMBAI-400 059, INDIA,
TELEPHONE NO-28397632, FACSIMILE NO- 28212110.

ORIGINAL

1165
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304/MUM/2004

11/3/2004 11 MAR 2004

304 | गुप्त | 2004
MUM

Received Rs. 3000/-	11/3/04
Observed/M.O.P. No. 2165	
Vide Entry No. 2165	
Register of Inventors	
Dr. Ratish	808

FORM 2

THE PATENTS ACT, 1970

(39 OF 1970)

PROVISIONAL SPECIFICATION

(See section 10)

A PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-10-OXO-5H-
DIBENZ[B,F]AZEPINE-5-CARBOXAMIDE

ORIGINAL

SUN PHARMACEUTICAL INDUSTRIES LTD.

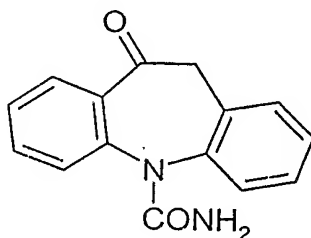
A company incorporated under the laws of India having their office at ACME
PLAZA, ANDHERI-KURLA ROAD, ANDHERI (E), MUMBAI-400059,
MAHARASHTRA, INDIA.

The following specification describes the nature of this invention.

304 | मुंबई | 2004
11 MAR 2004

A PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-10-OXO-5H-DIBENZ[b,f]AZEPINE-5-CARBOXAMIDE

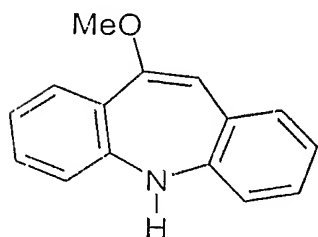
The present invention relates to a process for the preparation of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, compound of formula I, commonly known as oxcarbazepine (INN Name) used in therapy as an anticonvulsant.



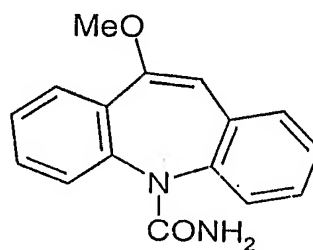
Formula I

BACKGROUND OF THE INVENTION

United States Patent No. 3,642,775 (Assigned to: Ciba Giegy Corporation) describes the preparation of compound of formula I from compound of formula II.



Formula II



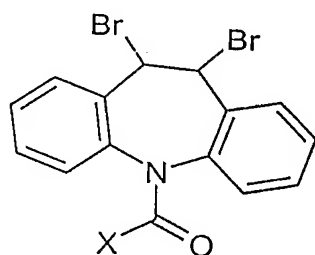
Formula III

The compound of formula II is reacted with phosgene in toluene and subsequently with ammoniacal ethanol to yield compound of formula III. Hydrolysis of compound of formula III with dilute mineral acid gives the desired product, compound of formula I.

United States Patent No. 5,808,058 (Assigned to M/s Trifarma) describes a different method for the synthesis of compound of formula I. Compound of formula II is subjected

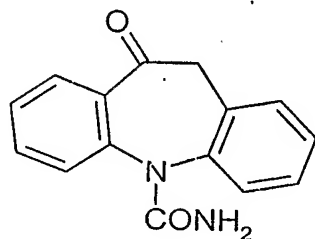
to direct carbamoylation with isocyanic acid generated in situ from cyanate and acid to generate compound of formula III which on acid hydrolysis furnishes the desired product.

Different routes for the preparation of compound of formula I are suggested in prior art. We have now developed a novel process for preparation of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, compound of formula I, in substantially pure form starting with compound of formula IV.



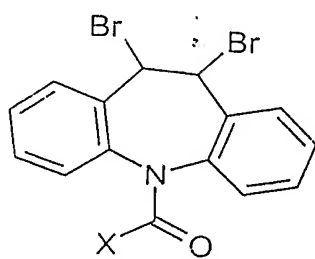
Formula IV (X=Cl, Br)

The present invention provides a process for preparation of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, compound of formula I, said process comprising

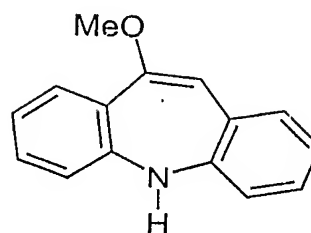


Formula I

- a. reacting compound of formula IV with excess of alkali metal methoxide to yield compound of formula II; and



Formula IV (X=Cl, Br)

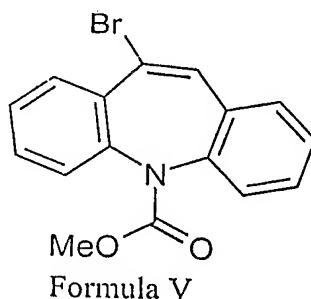


Formula II

- b. converting compound of formula II to compound of formula I.

According to the process of the present invention compound of formula II is prepared by reacting compound of formula IV with excess of alkali metal methoxide. The alkali metal methoxide can be selected from sodium methoxide, potassium methoxide and the like. The reaction may be carried out between 30-150°C.

In one embodiment of the process of the present invention when only slight excess of alkali metal methoxide is used, compound of formula V can be isolated which on further treatment with excess of alkali metal methoxide gives compound of formula II.



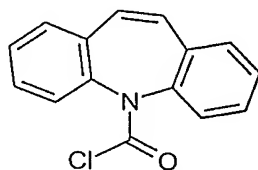
Formula V

In another embodiment of the process of the present invention compound of formula IV with excess of alkali metal methoxide directly yields the compound of formula II in one pot.

The compound of formula II is then converted to compound of formula I using any process known to a person skilled in the art.

The compound of formula I thus obtained may be further purified by recrystallization from solvent(s) to yield ICII grade material (purity not less than 99%). The solvent(s) may be selected from polar aprotic solvent, hydrocarbon solvent and their mixtures. Preferably mixture of polar aprotic solvent and hydrocarbon solvent in volume ratios varying from 1:0.5 to 1:5 is used. Optionally second recrystallization may be carried out from aqueous acidic solutions.

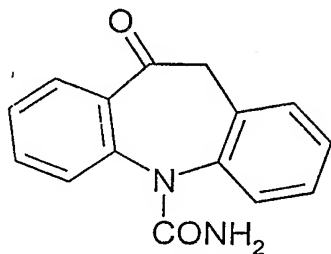
The starting material compound of formula IV may be prepared by any method such as brominating compound of formula VI, with bromine in acetic acid.



Formula VI

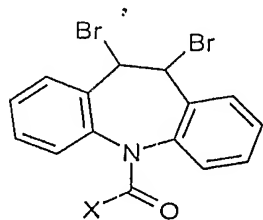
The summary of the present invention is defined below:

A. A process for preparing 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, compound of formula I, said process comprising

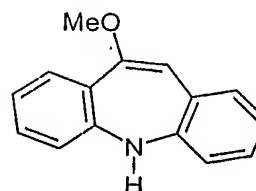


Formula I

- a. reacting compound of formula IV with excess of alkali metal methoxide to yield compound of formula II; and



Formula IV (X=Cl, Br)



Formula II

- b. converting compound of formula II to compound of formula I.

The invention is further illustrated but not restricted by the description in the following examples

Examples

Example 1

(a) Preparation of 10,11-Dibromo-10,11-dihydrodibenzo[b,f]azepine-5-carbonylchloride, compound of formula IV

1 Kg of Dibenzo[b,f]azepine-5-carbonylchloride is added to 5.0 L acetic acid and the mixture stirred for 5 minutes to get uniform slurry. 273 ml of liquid bromine is added dropwise by maintaining the batch temperature at 30-35⁰ C over a period of 1-2 hours. The reaction mixture is stirred for 1-2 hours at 32-35⁰ C followed by cooling to 15-20⁰ C. The reaction mixture is quenched by adding 3.3% w/v aqueous sodium thiosulfate solution. Cool the contents to 0-5⁰ C and stir for 2 hours. The product is filtered and washed with water and dried to get compound of formula IV.

(b) Preparation of Methyl-10-bromo-dibenz[b,f]azepine-5-carbamate, compound of formula V

1.037 kg of sodium methoxide solution is added to 1 litre of methanol. The mixture is cooled to 30-35⁰ C and 10,11-Dibromo-10,11-dihydrodibenzo[b,f]azepine-5-carbonylchloride, compound of formula IV, is added in lots under stirring by maintaining the temperature between 50-55⁰ C. The suspension is stirred at 50-55⁰ C for 45 minutes, to 1 hour. The reaction mixture is cooled to 30-40⁰ C and quenched by adding chilled DM water by maintaining the reaction mixture temperature at 30-40⁰ C.

The product is filtered and washed with DM water and dried to get compound of formula V.

(c) Preparation of 10-Methoxy-dibenz[b,f]azepine, compound of formula II

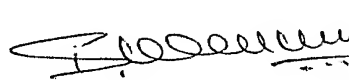
0.25 kg of Methyl-10-bromo-dibenz[b,f]azepine-5-carbamate, compound of formula IV, is added to 1.962 kg of 25% sodium methoxide solution under stirring at room

temperature. The reaction mixture is heated to 88-93°C and stirred at that temperature for 12-16 hours. The reaction mixture is cooled to 20-25°C and quenched by adding chilled water by maintaining temperature between 20-25°C. The product is filtered and washed with DM water and dried. The product obtained is further purified by using toluene: DMF (15 volumes: 1 volume) mixture to furnish a compound of formula II.

(d) Preparation of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, compound of formula I

10-Methoxy-dibenz[b,f]azepine, compound of formula II, is converted to 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, compound of formula I, by methods known in prior art.

Dated this 10th day of March, 2004



DILIP SHANGHVI

**CHAIRMAN AND MANAGING DIRECTOR
SUN PHARMACEUTICAL INDUSTRIES LIMITED.**